REMARKS

Claims 1, 2, 4-45, 47-60, 80, 81, 83-94, 99-109, 111, 112, 114-128, 131-132, 136, and 138 presently appear in this case. Claims 6-18, 21-37, 39-43, 45-51, 53-58, 79-94, 96-108, 110-134, 136 and 138-140 have been withdrawn from consideration. No claims have been allowed. The Office Action of March 4, 2010, has now been carefully studied. Reconsideration and allowance are respectfully urged.

The present invention is directed to compounds which combine an iron chelation moiety with other functional moieties, each of which is known to have beneficial effects of its own, either as a neutroprotector and/or as an inhibitor of apoptosis. This unique combination provides multifunctional compounds that can reduce excess local iron levels and, in addition, confirm neuroprotection and/or inhibit apoptosis by means which do not involve iron chelation. In the compounds of the present invention, the iron chelating function is provided by an 8-hydroxyquinoline moiety, a hydroxamate moiety or a pyridinone moiety. In addition to the iron chelating moiety, there is at least one additional moiety that imparts a neuroprotector function or that imparts combined antiapoptotic and neuroprotective function. The neuroprotective moiety is a L- or D-cysteine or L- or D-alanine residue, a neuroprotective peptide, a neuroprotective peptide fragment or an analog of

the neuroprotective peptide or neuroprotective peptide fragment. The moiety that imparts combined antiapoptotic and neuroprotective function is a propargyl group. The unique combination of the present invention provides multifunctional compounds which can reduce excess local iron levels and, in addition, confer neuroprotection and/or inhibit apoptosis by means which are not related to iron chelation *per se*. The invention also comprehends pharmaceutical compositions including such compounds as well as methods of use of such compounds.

The examiner has repeated and made final the restriction requirement, although the examiner cites totally new reasons for doing so. The examiner no longer relies on the Zhang article to show lack of unity of invention but now relies on Santiago (1997) and WO2000/074664 to allegedly show the same iron chelator and neuroprotective ability. This restriction requirement is again respectfully traversed.

First of all, it is requested that the examiner withdraw the finality of the restriction requirement in view of the fact that totally new reasons for showing lack of unity of invention are provided, to which applicant did not previously have an opportunity to respond.

With respect to the newly cited references that allegedly establish lack of unity of invention, it is noted

that the examiner has not provided a full citation or a copy of the Santiago (1997) publication. It is requested that the examiner officially cite it of record on an appropriate form PTO-892 and provide a copy to applicant. In the examiner's search strategy (a copy of which is of record in the PAIR records), there is a reference to Santiago et al. "Neuroprotective effect of the iron chelator desferrioxamine against MPP+ Toxicity on Striatal Dopamineric Terminals" *Journal of Neurochemistry,* 68:732-738 (1997). If this is the reference to which the examiner refers, then it is apparent from the title and abstract that it deals only with the iron chelator desferrioxamine. First of all, the present claims do not cover the use of desferrioxamine as the iron chelator. Secondly, the present claims make very clear that there must be separate moieties providing iron chelator effects and neuroprotective effects. While iron chelators may be known to have neuroprotective effects on their own, the present claims require the presence of a moiety other than the iron chelating moiety in order to provide additional neuroprotecting effects or the antiapoptotic/neuroprotecting effects. There is no such separate moiety in desferrioxamine. This reference thus does not show lack of unity of invention, does not show that any part of the present invention was available in the prior

art, and thus does not anticipate or make obvious any of the present claims.

Similarly, the PCT publication cited by the examiner shows only a compound with iron chelating ability but with no separate moiety that provides a neuroprotective effect. The closest compound of the present invention to the compound cited by the examiner requires the presence of a propargyl group attached the piperazine. There is no propargyl moiety in the compound cited by the examiner, nor is there any moiety other than the iron chelating moiety itself that provides any type of neuroprotective and/or antiapoptotic effect.

The special technical feature of the present claims relates to the bifunctional nature of the compounds of the present invention. Both an iron chelating moiety must be present as well as a separate and distinct neuroprotective and/or antiapoptotic moiety. This is made very clear by the way claim 1 was been presently amended. The present claims do not read on any compound that differs from the compound of the PCT publication by an ethyl versus a butyl moiety (as suggested by the examiner). Either a peptide or a cysteine or alanine residue must be present or a propargyl group. None of these are present in the PCT publications cited by the examiner. Accordingly, these references do not establish lack of novelty for the special technical feature present in the

present claims. Reconsideration and withdrawal of the restriction requirement is again respectfully urged.

The examiner states that a complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action. This requirement is respectfully traversed.

First of all, the present action is not a final rejection. Secondly, 37 CFR 1.144 states that claims that have been non-elected with traverse may remain in the case pending the filing of a petition, the filing of which may be deferred until after final action on or allowance of claims to the invention elected. Accordingly, as the new restriction requirement has been traversed and the finality thereof has been requested to be withdrawn, and as the present Official Action is not a final action and no appeal has been filed, there is nothing in the patent rules to require deletion of non-elected claims at this time. Reconsideration and withdrawal of this requirement are therefore respectfully urged.

Claims 1-5, 19, 20, 38, 44, 52, 59, 60, and 109 have been rejected under 35 USC 103(a) as being unpatentable over Warshawsky. The examiner states that Warshawsky teaches a Markush group of compounds, such as formula II, as iron chelators that offer neuroprotection that fully encompass the

instantly claimed compounds. Specifically, the examiner states that example 15 at column 12 is the compound that is exempted from the instant claims and the difference between the instant claims and the teachings of Warshawsky is that the specific compound of Warshawsky that fits within the instant claims is specifically exempted from the instant claims. The examiner states that it would have been obvious to make a differently substituted compound with the reasonable expectation of getting a compound with the same or similar properties. The examiner states that all of the claimed elements were known in the prior art and one skilled in the art would have combined the elements as claimed by known methods with no change in the respective functions and the combination would have yielded predictable results. This rejection is respectfully traversed.

Warshawsky is not relevant to the inventive step of the presently amended claims as it does not disclose, nor does it suggest, multifunctional compounds comprising, in addition to a moiety having iron chelation function, moieties that impart neuroprotective function. Claim 1 requires that the moiety imparting a neuroprotective function be selected from the group consisting of an L- or D- cysteine or an L- or D-alanine reside, a neuroprotective peptide, a neuroprotective peptide fragment, and an analog of said neuroprotective

peptide or neuroprotective peptide fragment. Neither does Warshawsky disclose or suggest a moiety that imparts combined antiapoptotic and neuroprotective function, i.e., a propargyl group.

None of the possible moieties which can be R^4 in the formula at column 3, lines 15-40, of Warshawsky is a neuroprotective or antiapoptotic/neuroprotective moiety as defined in the present claims. The only neuroprotective effect taught by Warshawsky is the effect of the iron chelator itself. The present claims are bifunctional in that there is a neuroprotective or antiapoptotic/neuroprotective moiety aside from the iron chelating moiety, which may itself have certain neuroprotective effects. It is important to note that Warshawsky refers to the compounds disclosed therein as "neuroprotective iron chelators," namely, the neuroprotective function is attributed solely to the iron chelator pharmacophore which, by chelating excess iron in the brain, prevents oxidative damages and neuronal cell death. The ability of the iron chelators to act as neuroprotectors by preventing lipid peroxidation in brain tissue is discussed in detail in the paragraph bridging columns 6 and 7 and in the background section of Warshawsky. For example, it is mentioned that oxidative stress caused by a selective increase in content of iron in the brain has been implicated in the

biochemical pathology of Parkinson's Disease, and it is assumed that chelation of excess iron may protect the neurons from further deterioration. Warshawsky does not mention anywhere ways by which neurodegeneration may be treated by means other than iron chelation.

On the other hand, in the multifunctional compounds of the present invention, the neuroprotective function may be provided by a cysteine or alanine reside or by the residue of a neuroprotective peptide, a neuroprotective analog or neuroprotective fragment thereof, and the combined apoptotic and neuroprotective function is preferably provided by a propargyl group (see page 9, lines 16-21 of the present specification). Thus, the instant compounds impart a neuroprotection effect attributed to certain moieties, as defined in amended claim 1, which function as neuroprotectors *per se* and do not chelate iron. Combined neuroprotection and antiapoptotic effect is attributed to a propargyl group, which also does not exert its effect by iron chelation. A person of ordinary skill in the art would not find the incentive in Warshawsky to modify the compounds disclosed therein to form improved neuroprotective function compounds by combining a iron chelation moiety with certain neuroprotective peptides or fragments thereof and/or with a propargyl moiety, all as described in the present application. Note that the compound

referred to by the examiner as being excluded by the present claims is not covered by the claims as presently amended.

As the compounds of the present invention are structurally and conceptually different from the compounds of Warshawsky, reconsideration and withdrawal of this rejection is respectfully urged.

Claims 1-5, 19, 20, 38, 44, 52, 59, 60 and 109 have been rejected under 35 USC 112, first paragraph, as failing to comply with the written description requirement. The examiner states that the instant specification does not adequately describe how the instantly claimed compounds offer antiapoptotic functions or a combined neuroprotective and antiapoptotic function. The examiner states that the specification discusses iron chelation and how that relates to neuroprotection and some discussion is presented about antioxidants but the examiner states that there is no written description for the antiapoptotic functions of the instantly claimed compounds. This rejection is respectfully traversed.

First of all, it is important that one does not misunderstand the present invention. It would be a misimpression if one were to believe that the compounds of the present invention are iron chelators first and most of all, and that based on their ability to chelate iron, they can confer neuroprotection and inhibit apoptosis. This would

clearly be wrong. As we have shown above, the present invention does not correlate antiapoptotic and neuroprotective functions with iron chelation *per se*. Rather, these functions are attributed to functional moieties selected from neuroprotective peptides, fragments and analogs, and to L- or D-cysteine or L- or D-alanine residues. The combined antiapoptotic and neuroprotective function is attributed to the propargyl group, preferably a propargylamine group.

The Biological Section, beginning at page 83 of the present specification and including examples 30-37, discloses the neuroprotection results and inhibition of cell death obtained with compounds of the invention comprising a neuroprotective peptide and/or a propargyl group. The compound HLA-20, comprising a propargylamine group, has been found effective in neuroprotection of P19 cells (Example 32), as well as serving as an antiapoptotic active agent in serum-deprived PC12 cells (Example 33). HLA-20 also inhibited MAO (Example 34) and promoted iron chelation in K562 cells (Example 31).

Example 32 describes neuroprotection of differentiated P19 cells obtained with compound M7, which comprises a neuroprotective peptide fragment. Example 34 describes *in vivo* inhibitory effects on MAO activity in rat brain obtained for the compounds M30 and M31, which comprise a

propargyl group. Thus, the present specification clearly describes neuroprotective functions or a combined antiapoptotic neuroprotective function in addition to iron chelating function in the compounds of the present invention. This fully satisfies the written description requirement of 35 USC 112. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 1-5, 19-20, 38, 44, 52, 59-60 and 109 have been rejected under 35 USC 112, first paragraph, as failing to comply with the enablement requirement. The examiner states that the state of the prior art is that iron chelators have not been linked to antiapoptotic functions and that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any antiapoptotic function on its face. This rejection is respectfully traversed.

As indicated above, applicant is not taking the position, and the specification does not state, that the present invention provides an antiapoptotic function because of its iron chelating function. The antiapoptotic function of the compounds of the present invention is provided by the propargyl group. This is not an iron chelating group. It is an antiapoptotic moiety. The present invention combines this antiapoptotic moiety with an iron chelating moiety in the same

compound. Thus, those of ordinary skill in the art would not consider that it violates the state of the art to believe that such compounds would have the function of each of these moieties. Indeed, as indicated above, the Biological Section of the specification establishes this with working examples. Contrary to the examiner's statement that there are no working examples of the instant compounds having antiapoptotic functions, the examiner's attention is invited to example 33, which is directly related to neuroprotection of PC12 cells against serum-deprivation induced apoptosis. The other examples discussed above are also relevant in this regard.

As explained above, the unique feature of the present compounds is the combination of an iron chelation function with other functional moieties, each of which is known to have beneficial effects of its own, either as neuroprotector and/or as inhibitor of apoptosis. This unique combination provides multifunctional compounds which can reduce excess local iron levels and, in addition, confer neuroprotection and/or inhibit apoptosis by means which do not involve iron chelation. Based on the results and the teachings disclosed in the present application, a skilled person would reasonably expect that, if certain compounds showed desired results *in vitro*, the other, similar compounds, would present such desired results as well. A skilled person

would also reasonably expect that if certain exemplifying compounds that were active *in vitro* showed corresponding *in vivo* activity, the other similar compounds would similarly be active *in vivo* as well. Evidence of *in vitro* and *in vivo* activity is present in the present specification as discussed above. Accordingly, there is insufficient reason for the examiner to disbelieve the broad statements in the present specification in this regard.

The claims presently being examined are compound claims and not method of use claims. As long as there is a single believable utility for the compounds of the present invention, then the utility requirement and the how-to-use requirement of 35 USC §112 have been satisfied. The examiner has not explained why he does not believe that the present compounds would work for even a single neuroprotective activity. There are no claims in the present application presently directed to the treatment of cancer.

For all of these reasons, reconsideration and withdrawal of this rejection are respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and

fully comply with 35 USC §112, reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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